

REMARKS

Claims 1, 5, 6, 9-15 and 17-23 are all the claims pending in the application.

Claim 14 is canceled.

Claims 1, 17, and 18 are amended to include the recitation of claim 14, reciting that the organic base comprises N-methylmorpholine. Claim 20 has also been amended to clarify the wording, and to incorporate formulas (1) and (2) from claim 1. No new matter is added.

Claims 19 and 20 are amended to delete the term "or the like." Claim 20 is further amended to delete a portion of the definition of R^2 , which was asserted to lack antecedent basis, i.e. "provided that said amino, mercapto, guanidyl, carboxyl, hydroxy and imidazolyl groups which may be present in R^2 and substituent groups contained therein are in a protected form." No new matter is added.

Claim 1 is further amended to correct what appears to have been an oversight in the Amendment of February 19, 2003, in which the definition of R^1 left out the phrase "optionally substituted saturated or unsaturated hydrocarbyl group." In this respect, the present amendment restores this term to its originally filed form. No new matter is added.

Claim 23 is added, reciting the method of claim 19 where Y is a carbon atom, $n=1$, and $p=1$. Support is found in base claim 17; no new matter is added.

Claim 20 is rejected as indefinite under 35 U.S.C. § 112, ¶ 2 for lack of antecedent basis for the term "provided that said amino, mercapto, guanidyl, carboxyl, hydroxy and imidazolyl groups which may be present in R^2 and substituent groups contained therein are in a protected form."

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In response, Applicants have amended claim 20 to delete this term. It is respectfully requested that the rejection be withdrawn.

Claims 1, 5, 9-13 and 17 are rejected under 35 U.S.C. §102(b) as anticipated by Urbanski et al, Polish Journal of Chemistry, vol. 58, pages 1227-1229 (1984) ("Urbanski"). Urbanski is asserted to disclose the synthesis of mixed sulfonic-carboxylic anhydrides from benzenesulfonyl chloride and various aromatic carboxylic acids. The amounts of carboxylic acid, benzenesulfonyl chloride (the carboxylic acid activating agent) and organic base (either pyridine or triethylamine) are asserted to be equimolar (0.02 mole).

In response, Applicants respectfully traverse. This rejection was discussed at length during the personal interview with the Examiner and Primary Examiner Raymond on April 25, 2003. At that time, the meaning of the word "add ___ to ___" was discussed in view of the specification, and Applicants offered to amend the claims to include language removing any possibility of confusion, although it was asserted then as it is now that the language is unambiguous.

Primary Examiner Raymond stated that the meaning of claims was clear in view of their plain meaning, the particular knowledge of those skilled in the field of chemistry, and the specification which expressly describes the unexpected results achieved when the carboxylic acid and organic base are *added to* an activating agent (Applicants' claims) rather than *adding* activating agent *to* carboxylic acid and organic base (cited art).

On pages 8-9, it is asserted that adding carboxylic acid and organic base are to an activating agent is no different than adding activating agent to carboxylic acid and organic base.

As support for this position, the Examiner relies on an ordinary dictionary definition of the word “add” and an analogy of adding coffee to cream.

The Examiner’s reasoning might properly be applied to those cases where the added elements remain unchanged after being added, as in the case of mathematics. However, the present claims are directed to a method for conducting a chemical reaction and the elements that are added are allowed to react and do not remain unchanged.

Applicants respectfully submit that it is legally improper to rely on an ordinary dictionary definition of “add” in this case to call into question the otherwise clear definition of the claim terms. See, for example, *AFG Indus. v. Cardinal IG Co.*, 239 F.3d 1239, 1247-48, (Fed. Cir. 2001)(observing that non-scientific dictionary definitions of ordinary words are rarely dispositive of their meanings in a technical context). MPEP 2111.01 makes clear that words in patent claims are given their ordinary meaning *in the usage of the field of the invention*.

The claims unambiguously recite “a method for producing acid anhydride which comprises *adding . . . to* a solution of” As one of skill in the art in the field of the present invention would know, the order of addition can be of grave importance, as reflected even in entry-level chemistry books that advise “adding acid to water,” rather than “adding water to acid.” For the Examiner’s convenience, Applicants would be happy to provide any number of references in the chemical field that draw distinctions between these exact phrases.

The analogy between the present claims drawn to a method for making acid anhydride, and adding coffee to cream is equally improper.

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In regard to the suggestion on page 7 of the Office Action that stage 2 of Urbanski discloses Applicants' claimed addition order of reactants, Applicants point out that Stage 2 in Urbanski does not correspond to Applicants' claimed synthesis reaction. In Stage 2, the carboxylic acid activating agent is an asymmetrical mixed acid anhydride, which is outside the scope of the carboxylic activating agent of formula (3) of the present invention.

As Applicants pointed out during the interview, stage 2 concerns the order of addition of the carboxylic acids, not the activating agent. This is reflected in the statement on page 1228 of Urbanski, which states: "The order of addition of both carboxylic acids had no significant effect on the yield of the unsymmetrical anhydrides." Not only does this not disclose the instant invention, it precludes any assertion that Urbanski might form the basis of an obviousness rejection, because it teaches away from the claimed method, implying that order of addition is not important. Had Urbanski experimented with the order of addition of all components, it might have been discovered otherwise.

Accordingly, the mathematical definition of "add" relied upon on page 7 of the Office Action is not germane. This issue has been addressed three times in response to three non-final office actions, in addition to an interview with the Examiner and his supervisor, and Applicants strenuously urge that this issue be put to rest.

Moreover, to clear any possible remaining uncertainty, the specification itself requires that the term "add ___ to ___" be construed according to the definition explained herein and not according to the mathematical dictionary definition, or the broad construction urged by the Examiner's coffee--cream analogy. Page 22 of the present specification states that if the

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activating agent is added to the acid and base, a different result is achieved, than if acid and base are added to activating agent. Specifically, in the former process--termed *conventional* in the specification, and thus not within the claimed process--acid anhydrides are produced as by-products and the selectivity in production of the mixed anhydride is low. Therefore, the construction of the term "add ____ to ____" is not only contrary to the plain meaning of the term within the chemical arts, but it is also contrary to the specification.

Urbanski discloses at page 1229 that benzenesulfonyl chloride was added to a mixture of a carboxylic acid and a tertiary amine in Stage 1. The carboxylic acid and a tertiary amine were not added to benzenesulfonyl chloride, as recited in the present claims. Urbanski does not disclose Applicants' claimed process, and therefore the cited art does not anticipate Applicants' claimed invention.

Moreover, there is no disclosure or teaching of a process of producing a mixed acid anhydride using the carboxylic acid of Applicants' formula (8).

Therefore, the amended claims are not anticipated by Urbanski.

The rejections over Fife, Benoiton, and Gaede are traversed for the same reason. Properly construed, Applicants' claims are not disclosed in the description of the conventional processes set forth in the cited art.

In response to the rejection over Applewhite, Applicants additionally point out that Applewhite does not disclose the use of N-methylmorpholine.

On page 9 of the Office Action, it is asserted that Applicants' experimental evidence of unexpected superiority resulting from the claimed process is not persuasive for two reasons.

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First, it is argued that the cited art is anticipatory, making evidence of unexpected results irrelevant. As a result of the response set forth in detail above, Applicants submit that experimental evidence of unexpected results is relevant, as the cited art can only be asserted under 35 U.S.C. § 103 (although no rejection under § 103 has been raised). Therefore, it is requested that the experimental data summarized in Table 1 of the specification be reconsidered.

In response to the Examiner's concern that the comparative data in the specification references carbonate, one skilled in the art would understand mixed acid anhydride to include carbonate. These are not different substances, as the Examiner urges. As explained in detail in the specification, Applicants have discovered the chemical mechanism by which by-products are reduced and selectivity is increased in the claimed mixed acid anhydride reaction. Experimental data of carbonate demonstrates this principle and the unexpected results achieved thereby.

Further, Applicants provide the Declaration of Takashi Miki which contains additional experimental evidence showing that Applicants' claimed process leads to an unexpectedly superior yield, as compared to the most similar example in Applewhite.

As set forth in the Declaration, by using N-methylmorpholine of the claimed process instead of triethylamine, as used in Applewhite, Applicants attain an unexpectedly high yield of 92.5%, as contrasted with a comparative yield of only 81.0%.

Therefore, even if a *prima facie* obviousness rejection were to be asserted, Applicants' claimed process yields unexpectedly superior results, as compared to the most similar example in the cited art, thereby rebutting any assertion of obviousness.

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For at least the reasons set forth above, the cited art does not render Applicants' claims unpatentable, and it is respectfully that the foregoing rejections be reconsidered and withdrawn.

Reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. The prior art rejections discussed herein were first asserted in the Office Action of September 18, 2002; the current Action is the most recent of a series of three non-final Office Actions. Applicants respectfully assert that this rejection is now stale, having been discussed at length, and it is respectfully requested that it be timely reconsidered and this application be put in condition for immediate allowance.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.


Respectfully submitted,

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Date: December 22, 2003



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Takashi MIKI et al.

Serial No.: 09/870,676

Group Art unit: 1624

Filed: June 1, 2001

Examiner: TUCKER, ZACHARY C

For: PRODUCTION OF MIXED ACID ANHYDRIDE
AND AMIDE COMPOUND

DECLARATION OF Takashi MIKI UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Takashi MIKI, a citizen of Japan, residing at 2-10-3, Sonehigashino-chou, Toyonaka-shi, Osaka, Japan do hereby declare and say that:

1. I am one of the joint inventors of the above-identified application;
2. I received a Master degree in chemistry from Nagoya University, Graduate School of Science, Department of Chemistry in March 1992;
3. Since 1996 up to now, I have been employed by Sumitomo Chemical Company, limited and engaged in the synthesis of pharmaceutical intermediate compounds;
4. I have read the Office Actions issued in the above-identified application and references cited therein; and
5. I conducted the following experiments to show the unexpected

results of the present invention over the teachings of the cited references, USP 3,264,281 to Applewhite et al, particularly Example VIII of column 9 where an equimolar amount of a carboxylic acid, a tertiary amine compound and carboxylic acid activating agent, or USP 3,264,281 in view of Int. J. Peptide Res. 42, 1993, 278-283 to Benoiton et al.

Experiment

Experiment I

A solution of 2.44g (0.0117mol) of carbobenzyloxyglycine (Z-Gly) and 1.18g (0.0117mol) of N-methylmorpholine in 18.7g of tetrahydrofuran was added dropwise in 1 hour to a solution of 1.29g (98% purity, 0.0117mol) of ethyl chlorocarbonate in 16.4g of tetrahydrofuran at $-7 \pm 2^\circ \text{C}$ under stirring and the resulting solution was stirred for 30 minutes at $-7 \pm 2^\circ \text{C}$. Then, 2.52g (0.0117mol) of L-phenylalanine methyl ester hydrochloride was added thereto at $-5 \pm 5^\circ \text{C}$, and subsequently a solution of 1.18g (0.0117mol) of N-methylmorpholine in 2.4g of tetrahydrofuran was added dropwise to the mixture in 30 minutes at $-5 \pm 5^\circ \text{C}$ and stirred for 3 hours thereafter at $-5 \pm 5^\circ \text{C}$.

After completion of the reaction, 56 g of ethyl acetate was added at -5 to 5°C , and 8.1 g of 1% hydrochloric acid was dropwise added at 5 to 10°C and stirred for 10 minutes, settled and separated. The obtained organic layer was washed with 12 g of an aqueous 9% sodium chloride solution, settled and separated. The obtained organic layer was washed with 11 g of an aqueous 5% sodium hydrogen carbonate solution at 15 to 30°C , settled and separated. After that, the organic layer was washed with 11 g of water at 15 to 30°C , settled and separated. The obtained organic

layer was evaporated in vacuo. To the obtained oil, toluene and tetrahydrofuran were added and then evaporated in vacuo to give 4.55g of an oil. It was found that the concentrated oil product contained the desired compound in an amount of 88.04wt% by LC analysis. Thus, the product, methyl N-carbobenzyloxyglycyl-L-phenylalaninate, was obtained as a pale-yellow oil in a yield of 92.5% in terms of Z-Gly.

Experiment II

An experiment was conducted in a similar manner as in Example I except that 1.18g (0.0117 mol) of triethylamine was used in place of N-methylmorpholine. 4.54g of a pale-yellow oil containing the desired compound in an amount of 77.29wt% was obtained. Thus, it was found that methyl N-carbobenzyloxyglycyl-L-phenylalaninate, was obtained as a pale-yellow oil in a yield of 81.0% in terms of Z-Gly.

Conclusion

As shown in the experimental results above, an amide compound was obtained unexpectedly in a yield of 92.5% in an embodiment of the present invention using N-methylmorpholine while the same amide compound was obtained in a yield of 81.0% in the method of Applewhite in which triethylamine was used as an organic base. From such unexpected improvement of the yield it can be concluded that the mixed anhydride was obtained unexpectedly improved yield in the presently claimed process as compared to the method of the reference(s).

I declare further that all the statements made herein of my own knowledge are true and that all statements made on information and belief are to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issued thereon.

This 17th day of December, 2003

Takashi Miki

Takashi MIKI